

REMARKS

Claims 54-78 were pending in this application when last examined. Claims 55-65, 67-68 and 70-73 have been canceled without prejudice. Claims 66, 69 and 74-78 have been amended and new claims 79-86 have been added.

Support for the amendments can be found in the specification and in the original claims as filed. No new matter has been added.

CLAIM REJECTIONS - 35 USC § 102

At page 2, item 6, the Office Action rejects claims 65, 66, 68, 73, 74 and 77 under 35 U.S.C. § 102(b) as anticipated by REGTOP et al. (US 5,466,824).

At page 5, item 15, the Office Action also rejects claim 76 under 35 U.S.C. § 102(b) as being anticipated by REGTOP. Applicant respectfully traverses these rejections.

The currently amended claims recite claim 77 as the primary independent claim. All other claims are dependent thereon.

Amended claim 77 is directed to a pharmaceutical composition wherein the active ingredient consists of indomethacin (INDO) and/or salts thereof in combination with a pharmaceutically effective amount of at least one metal and/or

corresponding salts. REGTOP fails to teach or suggest such compositions.

REGTOP describes a complex of indomethacin with divalent metals and tertiary or cyclic tertiary amide. The complex is formed by dissolving indomethacin and a salt of the divalent metal in a tertiary amide, and adding a C₁₋₄ alkanol or C₃₋₆ ketone to the solution to precipitate the complex (see, Abstract). REGTOP also disclose the potential use of copper, zinc, cobalt or nickel salts as the divalent metal salt, and most preferably cupric acetate monohydrate (see, column 3, lines 2-5, and column 4, lines 19-21). Indeed, the teachings of REGTOP, including all of the Examples, are limited to copper₂indomethacin₄ complexes formed in combination with a tertiary amide (i.e., [M]₂[indomethacin]₄[S]_n), for the purpose of analgesic and anti-inflammatory activities.

The REGTOP compound forms a complex of divalent metal, indomethacin and a tertiary amide, i.e., one single chemical structure including the INDO, divalent metal, and tertiary amide. The object of forming such a complex is to make the INDO physiologically available in a form having reduced side-effects on the gastric mucosa when administered orally. REGTOP teaches that not all metals can be used for the purposes disclosed, but only divalent metals, and essentially only copper. REGTOP also teaches the formation of a three component complex that includes tertiary amide.

In contrast to REGTOP, the presently claimed pharmaceutical composition consists of a combination of two independent active ingredients, INDO and at least one metal (claim 77). In particular, the metal is gold, selenium or bismuth (claim 78). This composition is distinct from the three component complex taught in REGTOP.

Furthermore, the oxidation states of gold include +1 (gold I) and +3 (gold III), while bismuth is only found at the oxidation states +3 and +5 (trivalent and pentavalent). Selenium can be divalent but can also have oxidation states of +6 and +4.

REGTOP, however, is limited to and requires a divalent metal (copper) and a tertiary amide formed into a complex (i.e., $[M]_2[indomethacin]_4[S]_n$). REGTOP fails to teach or suggest any type of pharmaceutical composition that does not include this type of divalent metal-INDO-amide complex.

For at least these reasons, REGTOP fails to teach or suggest, and does not anticipate, a pharmaceutical composition having the combination of elements as recited in claim 77, and in claims 66, 69, 74-76 and 78-86 dependent thereon. Accordingly, Applicant respectfully requests reconsideration and withdrawal of the rejection.

CLAIM REJECTIONS - 35 USC § 103

At pages 3-5, items 8-12, the Office Action rejects claims 69, 70, 75 and 78 under 35 U.S.C. § 103(a) as being

unpatentable. The Office Action rejects claims 69 and 70 as obvious over REGTOP in view of BERGE et al. (Journal of Pharmaceutical Sciences, 1977), rejects claim 75 as obvious over REGTOP in view of WILKINSON (Goodman & Gilman's The Pharmaceutical Basis of Therapeutics 10th ed., Chapter 1: Pharmacokinetics, 2001) and rejects claim 78 as obvious over REGTOP in view of TAYLOR et al. (US 6,303,295). Applicant respectfully traverses each of these rejections.

Each of these rejected claims depends from claim 77, and all of the above rejections rely on REGTOP as the primary reference. Thus, for at least the same reasons as provided in the comments above regarding the rejection under 35 U.S.C. § 102, REGTOP fails to teach or suggest a pharmaceutical composition wherein the active ingredient consists of indomethacin (INDO) and/or salts thereof in combination with a pharmaceutically effective amount of at least one metal and/or corresponding salts. Each of the cited secondary references, alone or in any combination, fails to remedy the deficient teachings of REGTOP. For at least this reason, REGTOP, BERGE, WILKINSON and/or TAYLOR fail to teach or suggest, and would not have rendered obvious, claims 69, 70, 75 and 78.

Furthermore, in regard to the TAYLOR reference and the rejection of claim 78, TAYLOR teaches "the importance of dietary selenium" only in view of its known antioxidant properties. TAYLOR fails to teach or suggest, however, that selenium has any

antiviral activity as contended in the Office Action. Moreover, REGTOP only describes the known anti-inflammatory properties of INDO but fails to teach or suggest anything regarding the antiviral activity of INDO. Thus, contrary to the position stated in the Office Action, one of ordinary skill in the art would not have any reason or motivation to combine INDO and selenium.

EXPERIMENTAL RESULTS

In further support of the patentability of the present claims, Applicant submits herewith in the Appendix an Experimental Report that shows the unexpected cooperative effects of indomethacin in combination with metal, within the scope of the present claims. The report shows that INDO antiviral activity is increased by the simultaneous treatment with low doses (from 10 to 100 uM) of metals. Preferred metals include gold, selenium and bismuth.

The study reports that the cooperative effect of INDO with these metals is due to the fact that they possess different mechanisms of antiviral activity. While the metal can inhibit viral gene expression and thus inhibit virus replication, INDO can inhibit virus protein synthesis. Evidence for the cooperative effects of INDO and metal on Herpes Simplex type 1 virus (HSV-1) is provided in the Examples. The results shown in Figure 2 demonstrate the increased anti-viral activity of INDO in

combination with bismuth citrate when compared to either INDO or bismuth alone.

In view of the amendments and the above remarks, REGTOP, BERGE, WILKINSON and/or TAYLOR, alone or in any combination, fail to teach or suggest, and would not have rendered obvious, claims 69, 70, 75 and 78. Accordingly, Applicant requests reconsideration and withdrawal of the rejection.

CONCLUSION

Entry of the above amendments is earnestly solicited. Applicant respectfully requests that a timely Notice of Allowance be issued in this case.

Should there be any matters that need to be resolved in the present application, the Examiner is respectfully requested to contact the undersigned at the telephone number listed below.

The Commissioner is hereby authorized in this, concurrent, and future submissions, to charge any deficiency or

credit any overpayment to Deposit Account No. 25-0120 for any additional fees required under 37 C.F.R. § 1.16 or under 37 C.F.R. § 1.17.

Respectfully submitted,

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APPENDIX:

The Appendix includes the following item(s):

- ☒ - SANTORO, Maria Gabriella, Experimental Report "Use of Indeomethacin and derivatives as broad-spectrum antiviral drugs and corresponding pharmaceutical compositions".